




Autism and Emotion: A Narrative Review

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Abstract

Autism spectrum disorder (ASD) includes a variety of childhood-onset and lifelong neurodevelopmental condition with an enduring impact on multiple domains of functioning characterized by persistent deficits in social communication, restricted and repetitive behavior interest, and activities. They often find it hard to recognize and control emotions but their emotional expression can be improved by various intervention techniques that in turn can help them understand and respond more appropriately to other people. Problems in the area on emotional reciprocity among individual with ASD involve recognizing, understanding, expressing, and regulating emotions. Their ability in emotional reciprocity is often improved with a comprehensive treatment approach, especially by focused emotional enhancement intervention. In this review, we followed the standard IMRAD (Introduction, Methods, Results, and Discussion) structure to critically examine the condition of autism and its relation with genetic mechanism, and how theories of emotion and theory of mind associated with persons with ASD, some of the widely used assessment tools and future research direction in the emotional development of individuals diagnosed with ASD by using the narrative review method. Records collected through research databases such as Scopus, PubMed, Web of Science, Medline, EBSCO and published books with ISBN (International Standard Book Number), and published test manuals were evaluated in-depth and summarized based on the subtopic of the proposed title. A critical theoretical analysis of the genetic mechanism of emotions, theories of emotions, and theory of mind was explained in connection with ASD.

Keywords

- ▶ autism
- ▶ emotion
- ▶ theories of emotion
- ▶ theory of mind

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Introduction

International Classification of Diseases, 11th revision (ICD-11), which was developed and released by the World Health Organization (WHO) in 2018, had given an updated criteria for autism spectrum disorder (ASD).¹ As per the updated guidelines of ICD-11, ASD is characterized as the continues deficiencies in the ability to initiate and continue the social interaction and communication with a range of restricted, repetitive pattern of behavior. The onset of this disorder occurs in early childhood and tends to continue throughout the person's life. It severely causes significant impairment in one's personal, family, and social life and becomes increasingly common in many parts of the world. The rise in diagnosis of autism impacts us all, seeking greater understanding and awareness of these complexities and comorbid condition.² Emotional and behavioral difficulties are the serious set of associated issues for an individual with ASD and these problems place a high burden on their family caregivers and clinical service providers. There had been numerous studies on the prevalence of autism,³⁻⁵ comorbid condition of ASD,⁶⁻⁸ effective interventions and treatments of ASD,⁹⁻¹³ and clinical drug trial¹⁴⁻¹⁷ that were conducted, and still, several studies have been performed to produce the vast knowledge on research in ASD. However, the emotional reciprocity of individual with ASD is yet to be explored in the medical and psychological field, for which this narrative review may shed a scientific spotlight.

As per WHO (2021)¹⁸ report, ~1 in 160 children has condition of autism spectrum worldwide. From the report of Sun and Allison,¹⁹ it was estimated that 14.8 in 10,000 were diagnosed with ASD in the Asia. Hossain et al,²⁰ in the identification of prevalence rate of ASD in South Asian countries like Bangladesh, India, Pakistan, Nepal, Sri Lanka, Bhutan, Maldives, Afghanistan, reported that 1 in 93 children were diagnosed with ASD. The first rigorous study of autism estimation in India by Arora et al²¹ found that ~1 in 100 children under the age of 10 has ASD and nearly 1 in 8 has at least one neurodevelopmental-related condition. Moreover, the incidence of autism is not increasing; the prevalence is increasing due to higher rate of diagnosis.

Materials and Methods

The articles for this review were collected from the published records of research databases such as Scopus, PubMed, Web of Science, Medline, EBSCO, published books with ISBN and standard test manuals. The records were collected from 1870 to 2020 and screened based on the following inclusion and exclusion criteria.

Inclusion criteria as follows:

1. Language of publication must be in English.
2. Original research and review articles, randomized control trial, and experimental studies.
3. Published books with ISBN and standard test manuals.
4. Peer-reviewed articles indexed in Scopus, PubMed, Web of Science, Medline, EBSCO databases.
5. Already been cited for scholarly reference.

Exclusion criteria as follows:

1. Non-English literatures.
2. Gray literatures.
3. Any Web site sources.
4. Nonpeer-reviewed sources such as newspaper, magazine articles.
5. Articles which are not previously cited for scholarly reference.

Screening and Selection

Approximately 50,000 articles were published in connection with autism between the period of 1870 and 2020. Based on the topic relevant, over 110 articles were selected carefully considering the inclusion criteria and critically examined as per the subtopic of the proposed review (►Fig. 1). Brief summary of the selected articles which are included in this study are given in ►Table 1.

Results

Autism and Its Associated Genetic Mechanisms in Relation with Emotion

ASD is a high genetic heterogeneous and possibly caused by the gene variations. Autistic features can occur as part of some genetic condition and it is estimated that 20% of the children with ASD will have a diagnosable genetic influence.²² Genetic defects involving the formation of synapses

Flow chart of screening of the articles

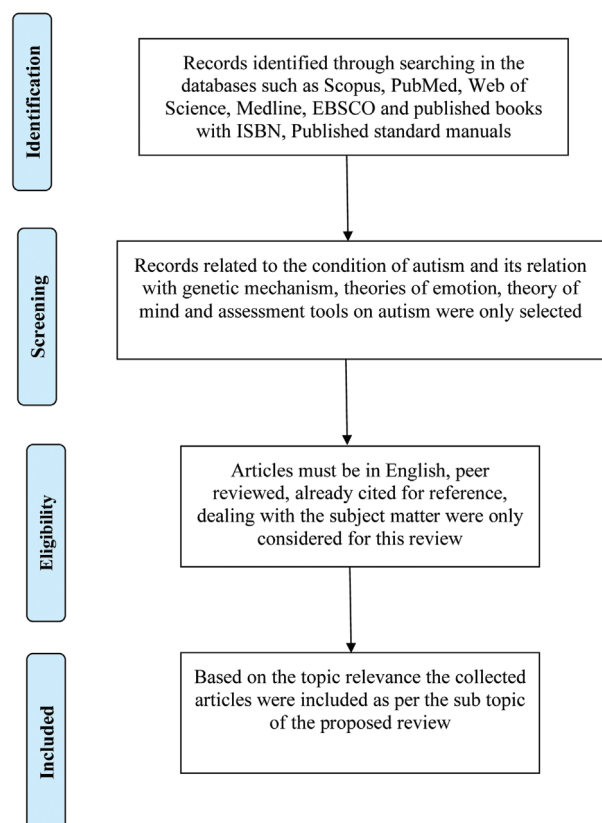


Fig. 1 Flowchart of screening of the articles

Table 1 Summary of the included article (In the order of subtopics)

Author(s) and Year	Research area/study measures	Brief summary
Autism and its associated genetic mechanisms in relation with emotion		
Scanlon et al (1979) ²⁶ Enoch et al (2003) ²⁷ Meyer-Lindenberg and Weinberger (2006) ³¹ Dapretto et al (2006) ²⁸ Yavich et al (2007) ²⁵ Rzhetsky et al (2007) ³² Pessoa (2010) ²⁹ Ursini et al (2011) ³⁰	<i>COMT</i> Catechol- <i>O</i> -methyltransferase	<i>COMT</i> is an enzyme that is involved in the degradation of the neurotransmitters (e.g., dopamine, epinephrine, and norepinephrine) and association of <i>COMT</i> Val158Met polymorphism might have genetic association with autism
Piven et al (1991) ³⁴ Lesch et al (1996) ³³ Tordjman et al (1997) ³⁵ Hariri et al (2002) ³⁷ Caspi et al (2003) ⁴⁰ Heinz et al (2005) ³⁸ Pezawas et al (2005) ³⁹ Hu et al (2006) ³⁶ Lonsdorf et al (2009) ⁴¹	<i>SLC6A4</i> Serotonin transporter	<i>SLC6A4</i> is a significant autism candidate gene. The <i>SLC6A4</i> mutation (HTT promoter polymorphism) has been linked to anxiety in the general population, and this, along with evidence of increased autism stress sensitivity and a higher incidence of anxiety disorder in autistic groups, has enhanced HTT concern in autism
Windle et al (1997) ⁴⁴ Kirsch et al (2005) ⁴⁵ Lee et al (2009) ⁴² Yamasue (2013) ⁵¹ Kirsch (2015) ⁴³ Auyeung et al (2015) ⁴⁷ LoParo and Waldman (2015) ⁵⁰ Koch et al. (2016) ⁴⁶ Yamasue and Domes (2018) ⁴⁹ Lucht et al (2019) ⁴⁸	<i>OXTR</i> Oxytocin receptor	Oxytocin is a primary transmitter of nervous behavior, especially in social situations, since it regulates the release of corticotrophin-releasing hormone. Single nucleotide polymorphisms (SNPs) in the <i>OXTR</i> gene have been linked to a lack of interest in relationships, infidelity, and social engagement. Autism spectrum disorder (ASD) symptoms have been associated to oxytocin receptor gene genotypes in several studies
Ahima and Harlan (1990) ⁵² Kovács et al (2000) ⁵³ Binder et al (2004) ⁵⁵ Ising et al (2008) ⁵⁷ Willour et al (2009) ⁵⁶ Bevilacqua and Goldman (2011) ²⁴ Criado-Marrero et al (2018) ⁵⁴	<i>FKBP51</i> Glucocorticoid receptor-regulating co-chaperone of stress proteins	Hsp90, FKBP51, or FKBP52, as well as Hsp70 and p23 heterocomplexes, bind to glucocorticoid receptor (GR). Functional mutations in the <i>FKBP5</i> gene have been associated with antidepressant responses, recurrence of mood disorders, attempted suicides in bipolar patients, and questionable regularization of stress-induced cortisol production. Due to its wide spectrum of amplification, <i>FKBP51</i> has been related to several medical conditions, including ASD
Davis (1992) ⁶⁷ Harmar and Lutz (1994) ⁶¹ Hashimoto et al (2006) ⁶² Falluel-Morel et al (2008) ⁵⁹ Ghzili et al (2008) ⁶⁰ Mounien et al (2009) ⁶³ Ressler et al (2011) ⁵⁸ Stroth et al (2011) ⁶⁴ Dias and Ressler et al (2013) ⁶⁵ Giustino and Maren et al (2015) ⁶⁹ Mercer et al (2016) ⁶⁶ Diener et al (2016) ⁶⁸	<i>PACAP</i>	The PAC1R binding of PACAP controls a variety of biological activities. Following fear training, rats showed increased expression of PAC1R in the amygdala, showing that it is important for emotional regulation. PAC1R may serve as a genetic modifier in ASD and provide a novel biomarker for stratifying individuals with ASD if it is validated in larger cohorts
Theories of emotion and theory of mind		
James (1884) ⁷⁶ Lange (1912) ⁷⁷ Gaigg (2012) ⁷⁴ Clarke (2015) ⁷⁸ Fitzpatrick et al (2018) ⁷⁵	James–Lange theory	This theory proposes that emotion occurs as a result of physiological reaction to certain events or stimuli. This theory is more suitable for neurotypical individual who perceives those events or stimuli appropriately and may not be connected to individual with neurodevelopmental disorders such as ASD

Table 1 (Continued)

Author(s) and Year	Research area/study measures	Brief summary
Newman et al (1930) ⁸² Sifneos (1973) ⁸⁴ Poquérousse et al (2018) ⁸³ Gu et al (2018) ⁷⁹ Vaughan et al (2020) ⁸⁰ Friedman (2010) ⁸¹	Cannon–Bard theory	This theory proposes that external events or stimuli induce <i>bodily reaction and emotion simultaneously</i> . From the reviews, it can be inferred that it is not evident that bodily reaction and feelings can raise simultaneously in the individual with ASD
Schachter and Singer (1962) ⁸⁷ Hadjikhani et al (2014) ⁸⁵ Meng et al (2017) ⁸⁶	Schachter–Singer theory	This theory proposes that external event or stimuli bring about physical arousal and cognitive reasoning by which we exhibit emotions. But due to the neurodevelopmental condition, it could not be related to <i>individual having the condition of ASD</i>
Tager-Flusberg (1999) ⁸⁸ Macari et al (2018) ⁸⁹	Cognitive appraisal theory	It is the subjective cognitive interpretation made by an individual to stimuli in the environment but autism itself is universally associated with cognitive impairment; hence, this theory may not applicable for individuals with the condition of ASD
Lazarus (1991) ⁹⁰ Green et al (1995) ⁹¹ Barrett et al (2007) ⁹²	Facial feedback hypothesis	It emphasizes that individual's facial expressions are connected to experiencing emotions but most individuals with ASD exhibit blend facial expression and have the condition of alexithymia; hence, it may not bring about theoretical connection in autism
Darwin (1872) ⁹³ Premack Woodruff (1978) ⁹⁵ Baron-Cohen et al (1985) ⁹⁷ Baron-Cohen (1991) ⁹⁶ Perkins et al (2010) ⁹⁴	Theory of mind	It is an understanding of emotion and social cognitive skills on one self and of others. This functional theory of mind is closely associated in people with ASD but even among the individual with autism, the variation in functioning found based on their severity level
Assessments in autism		
Schopler et al (1980) ¹⁰⁷ Le Couteur et al (1989) ¹⁰⁶ Rutter et al (2003) ¹¹⁰ Le Couteur et al (2003) ¹⁰⁴ de Bildt et al (2004) ¹¹³ Malhotra and Vikas (2005) ¹⁰¹ Lord et al (2008) ¹⁰³ Schopler et al (2010) ¹⁰⁸ Tine and Lucariello (2012) ⁹⁸ Lord et al (2012) ¹⁰⁵ Rudra et al (2014) ¹⁰² Juneja et al (2014) ¹¹¹ Wong and Singhal (2014) ¹¹⁴ Gilliam (2014) ¹⁰⁹ Raina et al (2015) ¹¹⁵ Hoogenhout and Malcolm-Smith (2017) ⁹⁹ Chauhan et al (2019) ¹⁰⁰ NIMH (2019) ¹¹²	The Autism Diagnostic Observation Schedule (ADOS) Autism Diagnostic Observation Schedule, 2 nd edition (ADOS-2) The Autism Diagnostic Interview-Revised (ADI-R) Childhood Autism Rating Scale (CARS-2) The Gilliam Autism Rating Scale (GARS-3) The Social Communication Questionnaire (SCQ) INCLIN Diagnostic Tool for Autism Spectrum Disorder (INDT-ASD) Indian Scale for Assessment of Autism (ISAA)	These are the few widely used assessment tools on autism that comprehensively measure the cognitive, behavior, social communication, speech and language communication, and emotional reciprocity and considered as gold standard

and branching of neurites result in a wide range of neuropsychiatric disorders including ASD.²³ Identifying the genetic mechanisms, which control emotion processing, can help to define the mechanisms with vulnerability to emotional problems in ASD. The five genes that are related or associated with emotions are *COMT* (catechol-O-methyltransferase), *SLC6A4* (serotonin transporter), *OXTR* (oxytocin receptor

gene), *FKBP5* (glucocorticoid receptor-regulating co-chaperone of stress proteins), and *PACAP* (pituitary adenylate cyclase-activating polypeptide).²⁴

COMT

COMT plays a major part in brain dopamine and norepinephrine catabolism. COMT enzyme has a significant function in

the prefrontal cortex where dopamine transporter is not abundant.²⁵ Val158Met is a common functional mutation that changes enzyme stability and is expected to decrease the dopamine levels in the prefrontal cortex.²⁶ Although associated with better cognitive performance, the Met158 allele results in higher anxiety and emotionality.²⁷ Met158 contributes to greater emotionality when it was examined by positron emission tomography and functional magnetic resonance imaging (fMRI). COMT Met/Met individuals exhibit improved reactivity and greater integration of the brain circuitry involved in generation and control of emotional responses.²⁸ The circuitry involves the prefrontal cortex and hippocampus, amygdala, orbitofrontal, and ventrolateral cortex. It is obvious that specific regions of the brain play a crucial role in emotion.²⁹ It is also suggested that, at the CpG dinucleotide produced by the Val158 allele, greater stress correlates with decreased methylation, likely modifying the expression of COMT and its associated traits.³⁰ We are unaware of the research associating Val158Met polymorphism with autism, although there is significant evidence of schizophrenia, and analysis of comorbidity suggests a genetic association with autism, schizophrenia, and bipolar disorder.^{31,32}

SLC6A4

It is primarily associated with anxiety, aggression, and attention. The efficacy of selective serotonin reuptake inhibitors, *SLC6A4*, is a strong autism candidate gene, and is a primary target in the therapeutic intervention of the anxiety and depression. 5-HTTLPR (serotonin-transporter-linked promoter region) is a specific polymorphism, located upstream of the *SLC6A4* gene.³³ *SLC6A4* variants were reported to be influencing the chronic autistic behavior. In addition, the documented correlation of an HTT promoter polymorphism with anxiety in the normal population combined with evidence of higher autism stress sensitivity and an elevated prevalence of anxiety disorder in the autism communities of individuals further intensified HTT concern in autism.^{34,35} Compared with the 16 repeat allele (L), a 14-repeat allele (S) has reduced transcriptional efficiency. In addition, the L allele often contains an A→G substitution, which makes it fundamentally comparable to the low-expression S allele by linking a defined transcription factor.³⁶ Studies suggested that the low transcription allele (S) enhanced amygdala activation after consciously viewing the emotional stimuli. Accordingly, connectivity experiments showed that the low-expression allele impaired the functional connection between the amygdala and the ventromedial prefrontal cortex and the pregenual cingulate, potentially impairing the prefrontal medial cortex's induction of fear.^{37–39} It was mentioned that low-transcription allele carriers appear more likely on being depressed and suicidal along with stressful experiences compared with the general population with two copies of the allele with high expression. The mechanism of effects of the reduction of 5-HTT functional genotypes on emotions includes enhanced development of conditioned responses to fear.^{40,41}

OXTR

Oxytocin is identified in very obvious forms, in all vertebrates and most invertebrates; it plays a significant function in the regulation of maternal activity and is among the few.^{42,43} Oxytocin regulates the hypothalamic release of corticotrophin-releasing hormone (CRH) that is engaged in the regulation of amygdalin stress response.^{44,45} It thus serves as the primary transmitter of anxious behavior, particularly under social circumstances.⁴⁶ At the genetic level, single nucleotide polymorphisms in the OXTR are linked with a lack of enthusiasm for relationships, adulterous relationship, and a general deficit in social contact.^{47,48} The nonverbal communication of facial expression, eye gaze, and gesture is found to be deficits in the social-emotional communication in ASD due to oxytocin effect; also several studies have employed that symptoms of ASD are associated with genotypes in OXTR.^{49–51}

FKBP5

Acute stress induces the hypothalamic release of the CRH from the paraventricular nucleus to the pituitary, where it activates the adrenocorticotrophic hormone (ACTH) secretion. CRH specifically, and by the action of ACTH, controls the release of adrenal cortisol, steroidogenesis, and catecholamine synthesis through the adrenal gland.²⁴ Cortisol, the stress hormone, targets two main receptors: a receptor of mineralocorticoids and a glucocorticoid receptor (GR). GR is particularly highly expressed in main regions of the hypothalamic-pituitary-adrenal (HPA) axis namely hippocampus, hypothalamus and amygdala.⁵² Negative feedback to block CRH release is necessary for normal functioning of the HPA axis, prohibiting persistent or excessive activation.⁵³ The response to stress with HPA is necessary for survival and helps to trigger a fight-or-flight response. Intracellularly, GR binds to a complex of multimeric chaperones. Intracellularly, GR binds to a complex of multimeric chaperones. Such heterocomplexes consist of Hsp90, FKBP51 or FKBP52, and Hsp70 and p23.⁵⁴ Functional mutation of the FKBP5 gene was associated with an antidepressant response, relapse of mood disorder,⁵⁵ attempted suicides in bipolar patients,⁵⁶ and inconclusive regularization of stress-induced cortisol secretion. Due to the plethora of functions and means of regulation of FKBP51 is associated with several medical conditions that include ASD.⁵⁷

PACAP

The PACAP and its selective PAC1 receptor have recently been shown to play a role in abnormal stress response underlying posttraumatic stress disorder (PTSD) in females.⁵⁸ PACAP regulates several biological processes by PAC1R binding, including neural development, cell stress response, glucose metabolism and feeding, neuroendocrine secretion enhancement in pituitary cells, and circadian clock regulation, and it was also found that Pac1r seems to play a key role in emotional regulation, as rodents showed enhanced expression of Pac1r in the amygdala after fear conditioning.^{59–64} At the functional level, the estrogen response element (ERE) sequence of the CC risk genotype compromises ER α binding,

inhibiting PAC1R transcription activation and resulting in decreased gene expression.⁶⁵ Since amygdala dysfunction is a signature characteristic of PTSD,^{66–68} findings indicate that decreased expression of PAC1R is related to a phenotype that results from impaired amygdala function. PAC1R may serve as a genetic modifier in ASD and may provide a novel biomarker for stratifying individuals with ASD if confirmed in larger cohorts.⁶⁹

From the literature, it had been identified that *COMT*, *SLC6A4*, *OXTR*, *FKBP5*, and *PACAP* genes directly or indirectly influence the autistic features of individuals and also any abnormalities in these functioning mechanisms cause the severe social–emotional impairments.

Autism and Theories of Emotions

There are several scientific studies that contributed to the autism research reveal the relationship between theories of emotion and emotional reciprocity state of the individual with ASD.^{70–73} In this category, we critically analyzed the famous theories such as James–Lange theory, Cannon–Bard theory, Schachter–Singer theory, cognitive appraisal theory, and facial feedback hypothesis and how it is not connected to the emotional regulation of individual with ASD.

James–Lange Theory

In 1884, William James first proposed that emotions have distinct bodily expression⁷⁴ and later it was independently developed by Carl Georg Lange in the year 1912 on the broad topic as “The Mechanism of the Emotions.”⁷⁵ In the modern psychology, the combination of these two theories is popularly known as James–Lange theory. According to this theory, emotions occur as a result of physiological reactions to a particular situation that means when an individual feels an external stimulus that results in physiological arousal. The emotional reaction followed by the physiological arousal is dependent on how the individual interprets those physiological reactions. The abnormal pain tolerance and high sensitivity to pain were noted in clinical observations on the individual with ASD,^{76,77} which is not usually seen in neurotypical individuals.⁷⁸ However, not all individuals with ASD have a higher threshold to sensory pain and so hypothetically it can be inferred that James–Lange theory might not be closely connected with emotional reciprocity of individuals with ASD.

Cannon–Bard Theory

Walter Bradford Cannon was a physiologist and best known for his work on homeostasis and Philp Bard was the student of Cannon and their work on emotion in the early 19th century is widely called as Cannon–Bard theory.⁷⁹ A disagreement of the James–Lange theory led to the development of the Cannon–Bard theory of emotion. According to Cannon–Bard, the thalamus plays a central role in emotion and it responds to an emotion-producing stimulus by sending impulses simultaneously to the cerebral cortex and other parts of the body and the emotions experienced are the result of simultaneous arousal of the cortex and the sympathetic nervous system. The theorists suggested that feeling and

physiological responses are two independent components of emotion. The emotional stimulus is processed in the brain region and then it independently creates both bodily reaction and feelings that were highly criticized in that era.⁸⁰ This theory cannot be associated with the individual with ASD because most individuals with ASD suffer from the condition called alexithymia.⁸¹ Alexithymia is a state of inability to identify and explain the emotional experience of one’s self or others.⁸² As per Diagnostic and Statistical Manual of Mental Disorders, 5th edition [DSM-V] by American Psychiatric Association), one of the major diagnostic criteria for ASD is deficits in social–emotional reciprocity.

The first study on real facial expression of pain to analyze the neural correlates of the autonomic empathic process in normal individuals with individual diagnosed with ASD shows no significant differences in brain activation during the perception of pain experienced by participants of both the groups, but they found individual with ASD represented empathy to overcome the personal overarousal and distress that lead to the inappropriate empathetic behavior.⁸³ The neurotypical individual may show appropriate bodily reaction and feelings as the result of emotion, but not all individual with ASD can express the same. Even the study by Meng et al demonstrate low autism spectrum quotient (AQ) individual responds more accurate in understanding others painful emotions when compared with high AQ individuals.⁸⁴ So, the hypothetical understanding would be that all individuals are capable of perceiving external stimulus irrespective of their neurological condition; it is not evident that bodily reaction and feelings can raise simultaneously in the individual with ASD.

Schachter–Singer Theory

A theory proposed by Schachter and Singer in the year 1962 explains that emotions were thought to result from the combination of two factors or components that involves the state of general physiological arousal and a cognitive explanation for that particular arousal which leads to the subjective experience of the emotion; hence, it has been addressed as two-factor theory.⁸⁵ Due to the neurological condition, most individuals with autism have difficulties in cognitive and social communication that interfere in their cognitive interpretation.⁸⁶ They may not only indicate a proper emotional response to the particular stimuli but also muted response to a threat.⁸⁷ Neurotypical individual cognitive interpretation to physiological arousal would be high and noncomparable to the individual with a neurologically atypical condition such as ASD.

Cognitive Appraisal Theory

According to cognitive appraisal theory of emotion, the cognitive appraisal mediates between the stimulus and the emotional response and it is often immediate and unconscious.⁸⁸ The sequence of events involves the stimulus followed by the thought that results in the simultaneous experience of physiological arousal and emotion. In contrast to the two-factor theory emotion, Lazarus argued that appraisal precedes cognitive labeling, simultaneously

stimulating both the physiological arousal and the emotional experience itself. But the condition of autism itself universally associated with cognitive impairment of varying degrees.⁸⁹ Hence, similar to the above theories of emotion, cognitive appraisal theory might not be closely connected with non-neurotypical individuals.

Facial Feedback Hypothesis

The facial feedback hypothesis states that an individual's facial expressions are connected to experiencing emotions. The idea that awareness of bodily experiences is the basis of emotion.⁹⁰ On the other hand, Darwin in 1872 investigated the way in which animals use facial expression and suggested facial feedback hypothesis in which he wrote that expression of an emotion intensifies it and suppression softens the emotion.⁹¹ If a person knows that the facial expressions are the ones, he or she associates with being sad, the person experiences the feeling of sadness. The contraction of facial muscle communicates what a person is feeling to oneself and others. A study was conducted to examine the mirror neuron abnormalities in children with autism, in which high functioning children with autism and matched control group underwent a fMRI while imitating and observing the emotional expression of others. Both the group performed the task equally well. However, children with autism showed no activity of the mirror neuron in the inferior frontal gyrus (pars opercularis). The dysfunction of the mirror neuron in children with autism may cause the social deficits such as deficits in imitation, theory of mind, and social communication and it is evident that autism individual finds it hard to understand the facial expression.⁹²

Theory of Mind and Autism

The term "Theory of mind" was first coined by an US psychologist, David Premack, in one of his articles as the ability to attribute mental states, opinion, desire, emotions, and knowledge from oneself to others. Theory of mind is necessary to understand that others have beliefs, desires, intentions, and perspectives that are different from one's own.⁹³ Premack conducted an experiment to check the presence of theory of mind in the chimpanzee. The results of the experiment suggested that the chimpanzee was able to understand the intentions, desires and emotions of the person shown in the videotapes. The theory of mind holds an assumption that each person has a mind of their own and each human can experience the presence of their own mind through reflection and introspection of one's own thoughts and behaviors. An individual does not have direct access to understand the mind of another person. However, it is possible to understand how another person's mind works through behavioral observation. Each individual's mind is unique and it is shaped by their environment, personal experience, and interactions with other humans. Understanding the intentions of another person is a determinant for understanding the mind of another person because intention represents an individual's mental states and personal events.⁹⁴ A study conducted by Baron-Cohen et al, where they believed that children with autism have deficit in

their "theory of mind" capacity due to which they are unable to represent their beliefs to others and predict other persons behavior.⁹⁵ Deficit in the theory of mind can also have difficulties in understanding other persons perspective and difficult time with social reciprocity. A study conducted by Tine and Lucariello to differentiate the theory of mind among children with autism and Asperger's syndrome. A battery of interpersonal theory of mind and social theory of mind was administered to 39 children with autism and 34 children with Asperger's syndrome. The results of this study indicated that for both groups of children, the theory of mind differentiated and interpersonal theory of mind was stronger than the social theory of mind. However, children with autism score lower on measures of the social theory of mind in comparison to Asperger's syndrome.⁹⁶

Hoogenhout and Malcolm-Smith in 2017 examined the severity level in autism by assessing the theory of mind capacity that predicted the type of school children with ASD attended. Using the hierarchical cluster analysis, the theory of mind capacity was grouped into three clusters:

1. Early developing theory of mind, which includes the ability to understand pretend play, desires, and perception knowledge.
2. False belief reasoning, which includes the ability to understand false belief reasoning, deceptive hiding, explanation of action along with cluster 1 abilities.
3. Sophisticated theory of mind understanding, which includes the ability to differentiate lie and joke along with cluster 1 and 2 abilities.

These clusters corresponded to severe, mild, and moderate signs of ASD, respectively. Children belonging to cluster 1 attended autism-specific school, cluster 2 attended both autism-specific and special school, and cluster 3 children attended a special school and mainstream schools for better social emotional understanding.⁹⁷

From the collective perceptive on theories of emotion and theory of mind, it can be inferred that individual with ASD finds it hard to perform the emotional reciprocity and the general theories on emotion may be adequate for the neurotypical individuals. Besides the fact that individual with ASD not to be compared with a neurotypical individual for emotional reciprocity, notable research studies show the significant improvement in the individual with ASD in their emotional state through focused interventions.

Assessment and Autism

Researchers have studied the prevalence of autism and discussed the difficulties in getting its estimates.⁹⁸⁻¹⁰⁰ Among them, the lack of uniformity in the application of fully validated and translated ASD diagnostic tools takes priority.^{101,102} There are numerous measures related to autism, developed in various countries that are being used for screening and diagnosis, but their functionality and reliability vary according to different research studies and some have remained questionable. Some of the widely used ASD assessments include Autism Diagnostic Observation Schedule (ADOS), Autism Diagnostic Interview-Revised

(ADI-R), Childhood Autism Rating Scale (CARS), Gilliam Autism Rating Scale (GARS), and Social Communication Questionnaire (SCQ). Better suited for the Indian population are the INCLIN Diagnostic Tool for Autism Spectrum Disorder (INDT-ASD) and Indian Scale for Assessment of Autism (ISAA).

To give an overview of the few widely used scales on autism assessment and the importance of assessing comorbid difficulties especially social–emotional reciprocity, a few measures are briefed in the following text.

The ADOS by Lord et al.¹⁰³ and the ADI-R by Le Couteur et al.¹⁰⁴ have long been considered as the “gold standard” in diagnostic evaluations for autism, particularly when combined with clinical judgment.¹⁰³

ADOS-2¹⁰⁵ is a structured, standardized assessment of communication, social interaction, and play or imaginative use of materials for individuals who have been referred because of possible autism or autistic spectrum disorders. Communication observations include vocalizations, using words and phrases; it also shows whether the individual uses functional, social, and gestural communication. Reciprocal social interaction measures elements like eye gaze and facial expression (response to name call, presence of social smile). Stereotyped behaviors and restricted interests assess sensory processing issues and interests such as hand flapping and other repetitive movements. The imaginative play describes the individual's ability to use symbolic imitation (pretend play). The ADOS-2 includes five modules—toddler module (12–30 months); module-1 (above 31 months, do not consistently use phrase speech), module-2 (any age who use phrase speech but not verbally fluent), module-3 (verbally fluent children and young adolescents), and module-4 (verbally fluent older adolescents and adults). Based on the expressive language level and chronological age, a module is chosen to be administered.¹⁰³

The ADI-R is another widely used semistructured diagnostic interview to assess behaviors related to autism or autistic spectrum disorders. The ADI-R is a shorter version of the original interview¹⁰⁶ and is designed for adults and children with a chronological age of at least 2 years old and a mental age above 2 years. Composed of 93 questions, the ADI-R focuses on three functional domains—language/communication (speech development, appropriate word use, ability to sustain conversation); reciprocal social interactions (interacting with others, showing or interpreting emotions); and restricted, repetitive, and stereotyped behaviors and interests (fixation on unusual items, irrational hand flapping or repeating phrases out of context). It also contains questions about the child's early development such as his/her family background, developmental milestones, and other clinically relevant behaviors such as aggression, self-injury, and possible epileptic features.¹⁰⁴

An extensively used rating scale for the detection and diagnosis of autism is the CARS by Schopler et al.¹⁰⁷ The most recent version is the second edition—CARS-2, which consists of 14 domains that assess behaviors associated with autism and a 15th domain that rates general impressions of autism. It consists of three forms: Standard Version Rating

Booklet (CARS2-ST) for use with individuals younger than 6 years of age and those with communication difficulties or below-average estimated IQs; High-Functioning Version Rating Booklet (CARS2-HF) for assessing individuals older than 6 years of age and with IQ scores above 80 and Questionnaire for Parents or Caregivers (CARS2-QPC) that gathers information of the individual's early development; social, emotional, and communication skills; repetitive behaviors; play and routines; and unusual sensory interests from the parents or caretakers. The 14 categories evaluated in CARS-2 include relating to people, imitation, emotional response, body use, object use, adaptation to change, visual response, listening response, taste, smell, and touch response and use, fear, or nervousness, verbal communication, nonverbal communication, activity level, and consistency of intellectual response.¹⁰⁸

The Gilliam Autism Rating Scale, currently at its third edition (GARS-3)¹⁰⁹ is another screening tool for ASD intended for use in individuals between ages 3 and 22. It assists teachers, parents, and clinicians in identifying autism in individuals and estimating its severity. The instrument consists of 58 items describing the characteristic behaviors of persons with autism grouped into six subscales of restrictive/repetitive behaviors, social interaction, social communication, emotional responses, cognitive style, and maladaptive speech.¹⁰⁹

The SCQ is another well-known screening instrument designed to evaluate communication skills and social functioning in children suspected of having ASD. The questions on the SCQ were developed based on items from the Autism Diagnostic Interview¹⁰⁶ and suitable for individuals over 4 years of age and have a mental age of 2 years and above. The questionnaire consists of two forms—lifetime and current—each composed of just 40 yes-or-no questions that can be given directly to the parent, who can answer the questions without supervision. While the lifetime form focuses on the child's entire developmental history, the current form looks at the child's behavior over the most recent 3-month period. The former identifies if the individual has to be referred for a more complete evaluation and the latter produces results that can be helpful in treatment planning, educational intervention, and measurement of change over time.¹¹⁰

The INDT-ASD is used as a screening tool to identify the presence of ASD and further understand where the individual falls in the spectrum. It is administrable on children from age 2 to 9 years; this tool is based on both history from primary caregivers and direct observation of the child. It has two sections: Section A has 29 symptoms/items and Section B contains 12 questions corresponding to B and C domains of DSM-IV-TR (social interaction, communication and restricted interests), time of onset, duration of symptoms, score, and diagnostic algorithm.¹¹¹

The ISAA used for diagnosing and measuring the severity of autism. It enables clinicians to quantify the severity of autistic symptoms so as to enable measurement of associated disability. The ISAA was developed based on CARS and has 40 items divided under six domains—social relationship and reciprocity; emotional responsiveness; speech, language and communication; behavior patterns; sensory aspects

and cognitive component. The result from the scale will indicate the mild, moderate, and severe functioning level of individual with ASD.¹¹²

Discussion

Over a decade of medical research, more than hundreds of genes had been identified and found to contribute to the deficits in social, behavior, and cognitive function of the individual. In autism, *COMT*, *SLC6A4*, *OXTR*, *FKBP5*, and *PACAP* genes are found to have a connection with emotional deficiency. From the collective literature, this narrative review empathizes the incongruence of the theories of emotion and theory of mind in relation with condition of ASD and some of the gold standard autism assessment tools that can be used clinically for the therapeutic intervention evaluation and certification of the individual with ASD.

Implication and Future Direction for Research

The cognitive and behavioral aspects of treating children with ASD by various intervention techniques provided significant improvement in their normal functioning. The advanced research performed in the medical field on autism contributed a lot in terms of accurate diagnosis and to find the level of functioning such as mild, moderate, or severe. All of the above yielded theoretical and empirical evidence for the effort performed over the decade by numerous mental health professionals, but, still, it does not provide the comprehensive treatment outcome because of the minimal focuses on emotional reciprocity. Children with autism frequently find it hard to perceive and control emotions. Their ability in the area of emotional reciprocity can be improved, which can assist them with comprehension and react in an appropriate way to different people. As of now, no treatment has been appeared to cure ASD, yet a few interventions have been developed and implemented for the benefit of children with ASD. These interventions may reduce symptoms, improve cognitive ability and daily living functioning, and boost the capacity of the children to work and participate in the social gathering. Research shows that early intervention treatment can altogether improve a child's development, which we theoretically evaluated in the most important domain on emotion. Enhancing emotion among individuals with autism is time-consuming, but it is effective in decreasing various issues, such as behavior problems and aggression, psychiatric symptoms like anxiety and depression and it also decreases functional impairments across settings like community, work, school. To decrease such issues, individuals with ASD should be able to regulate their emotions. This occurs only when the individual can recognize and understand their emotions. Hence, this review will theoretically support and influence the future studies related to emotional reciprocity and regulation for the better therapeutic plan.

Clinical and Research Implication

Autism research is vital for individual currently diagnosed and as well as for those with clinical symptoms of

neurodevelopmental condition. The in-depth critical literature reviews such as the connection between autism and emotion will shed light on understanding emotional reciprocity level, identifying emotional problems, developing effective intervention strategies for those with the condition of ASD. Most of the theories are expected to be proved in the form of experiment and need further validation for scientific justification. The arguments and scientific evidence of emotional related theories that are supporting and nonsupporting the condition of autism are discussed here for the further clinical understanding. The behavioral therapists and clinical psychologists who work and develop appropriate intervention technique can consider these aspects on emotion and incorporate appropriate methods to address the emotional need of people with autism.

Conclusion

This comprehensive review article emphasizes the factors of the genetic mechanism that influence autistic features, also irreconcilable of theories of emotion and theory of mind in relation to individual with ASD. The broadly used autism assessment scales and their domains are elaborated. Most importantly, the future need for the research in emotional area on autism is briefly explained.

Conflict of Interest

None declared.

References

- 1 World Health Organization. International classification of diseases for mortality and morbidity statistics, 11th Revi. Accessed August 10, 202 at: <https://icd.who.int/browse11/l-m/en>
- 2 Kopetz PB, Endowed ED. Autism worldwide: prevalence, perceptions, acceptance, action. *J Soc Sci* 2012;8:196–201
- 3 Matson JL, Worley JA, Fodstad JC, et al. A multinational study examining the cross cultural differences in reported symptoms of autism spectrum disorders: Israel, South Korea, the United Kingdom, and the United States of America. *Res in Aut Spec Dis* 2011;5:1598–1604
- 4 Rice CE, Rosanoff M, Dawson G, et al. Evaluating changes in the prevalence of the autism spectrum disorders. *Public Health Rev* 2012;34(02):1–22
- 5 Christensen DL, Baio J, Van Naarden Braun K, et al; Centers for Disease Control and Prevention (CDC) Centers for Disease Control and Prevention (CDC). Prevalence and characteristics of autism spectrum disorder among children aged 8 years—autism and developmental disabilities monitoring network, 11 Sites, United States, 2012. *MMWR Surveill Summ* 2016;65(03):1–23
- 6 Mannion A, Leader G. Comorbidity in autism spectrum disorder: a literature review. *Res in Aut Spec Dis* 2013;7:1595–1616
- 7 Doshi-Velez F, Ge Y, Kohane I. Comorbidity clusters in autism spectrum disorders: an electronic health record time-series analysis. *Pediatrics* 2014;133(01):e54–e63
- 8 Romero M, Aguilar JM, Del-Rey-Mejías Á, et al. Psychiatric comorbidities in autism spectrum disorder: A comparative study between DSM-IV-TR and DSM-5 diagnosis. *Int J Clin Health Psychol* 2016;16(03):266–275
- 9 Corsello CM. Early intervention in autism. *Infants Young Child* 2005;18:74–85
- 10 Kasari C, Patterson S. Interventions addressing social impairment in autism. *Curr Psychiatry Rep* 2012;14(06):713–725

- 11 DeFilippis M, Wagner KD. Treatment of autism spectrum disorder in children and adolescents. *Psychopharmacol Bull* 2016;46(02):18–41
- 12 Pasco G. The value of early intervention for children with autism. *Pediatr and Chil Heal* 2018;28:364–367
- 13 Sagayaraj K, Gopal CNR, Karthikeyan S. The efficacy of technology and non-technology based intervention for children with autism spectrum disorder: a meta-analysis. *Inter J Inno Sci and Res Tech* 2020;5:863–868
- 14 Aman MG, Novotny S, Samango-Sprouse C, et al. Outcome measures for clinical drug trials in autism. *CNS Spectr* 2004;9(01):36–47
- 15 Posey DJ, Stigler KA, Erickson CA, McDougle CJ. Antipsychotics in the treatment of autism. *J Clin Invest* 2008;118(01):6–14
- 16 Hampson DR, Gholizadeh S, Pacey LKK. Pathways to drug development for autism spectrum disorders. *Clin Pharmacol Ther* 2012;91(02):189–200
- 17 Ghosh A, Michalon A, Lindemann L, Fontoura P, Santarelli L. Drug discovery for autism spectrum disorder: challenges and opportunities. *Nat Rev Drug Discov* 2013;12(10):777–790
- 18 World Health Organization. News room, Fact sheet, Detail – Autism Spectrum Disorder. 2021 Jun 1. (Cited 2021 Jul 1); Accessed Aug 09, 2021 from <https://www.who.int/news-room/fact-sheets/detail/autism-spectrum-disorders>
- 19 Sun X, Allison C. A review of the prevalence of autism spectrum disorder in Asia. *Res Autism Spectr Disord* 2010;4(02):156–167
- 20 Hossain MD, Ahmed HU, Jalal Uddin MM, et al. Autism spectrum disorders (ASD) in South Asia: a systematic review. *BMC Psychiatry* 2017;17(01):281
- 21 Arora NK, Nair MKC, Gulati S, et al. Neurodevelopmental disorders in children aged 2–9 years: population-based burden estimates across five regions in India. *PLoS Med* 2018;15(07):e1002615
- 22 Rylaarsdam L, Gumez-Gamboa A. Genetic causes and modifiers of autism spectrum disorder. *Front Cell Neurosci* 2019;13:385
- 23 Hori K, Nagai T, Shan W, et al. Heterozygous disruption of autism susceptibility candidate 2 causes impaired emotional control and cognitive memory. *PLoS One* 2015;10(12):e0145979
- 24 Bevilacqua L, Goldman D. Genetics of emotion. *Trends Cogn Sci* 2011;15(09):401–408
- 25 Yavich L, Forsberg MM, Karayiorgou M, Gogos JA, Männistö PT. Site-specific role of catechol-O-methyltransferase in dopamine overflow within prefrontal cortex and dorsal striatum. *J Neurosci* 2007;27(38):10196–10209
- 26 Scanlon PD, Raymond FA, Weinshilboum RM. Catechol-O-methyltransferase: thermolabile enzyme in erythrocytes of subjects homozygous for allele for low activity. *Science* 1979;203(4375):63–65
- 27 Enoch MA, Xu K, Ferro E, Harris CR, Goldman D. Genetic origins of anxiety in women: a role for a functional catechol-O-methyltransferase polymorphism. *Psychiatr Genet* 2003;13(01):33–41
- 28 Dapretto M, Davies MS, Pfeifer JH, et al. Understanding emotions in others: mirror neuron dysfunction in children with autism spectrum disorders. *Nat Neurosci* 2006;9(01):28–30
- 29 Pessoa L. Emergent processes in cognitive-emotional interactions. *Dialogues Clin Neurosci* 2010;12(04):433–448
- 30 Ursini G, Bollati V, Fazio L, et al. Stress-related methylation of the catechol-O-methyltransferase Val 158 allele predicts human prefrontal cognition and activity. *J Neurosci* 2011;31(18):6692–6698
- 31 Meyer-Lindenberg A, Weinberger DR. Intermediate phenotypes and genetic mechanisms of psychiatric disorders. *Nat Rev Neurosci* 2006;7(10):818–827
- 32 Rzhetsky A, Wajngurt D, Park N, Zheng T. Probing genetic overlap among complex human phenotypes. *Proc Natl Acad Sci U S A* 2007;104(28):11694–11699
- 33 Lesch KP, Bengel D, Heils A, et al. Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. *Science* 1996;274(5292):1527–1531
- 34 Piven J, Chase GA, Landa R, et al. Psychiatric disorders in the parents of autistic individuals. *J Am Acad Child Adolesc Psychiatry* 1991;30(03):471–478
- 35 Tordjman S, Anderson GM, McBride PA, et al. Plasma beta-endorphin, adrenocorticotropin hormone, and cortisol in autism. *J Child Psychol Psychiatry* 1997;38(06):705–715
- 36 Hu XZ, Lipsky RH, Zhu G, et al. Serotonin transporter promoter gain-of-function genotypes are linked to obsessive-compulsive disorder. *Am J Hum Genet* 2006;78(05):815–826
- 37 Hariri AR, Mattay VS, Tessitore A, et al. Serotonin transporter genetic variation and the response of the human amygdala. *Science* 2002;297(5580):400–403
- 38 Heinz A, Braus DF, Smolka MN, et al. Amygdala-prefrontal coupling depends on a genetic variation of the serotonin transporter. *Nat Neurosci* 2005;8(01):20–21
- 39 Pezawas L, Meyer-Lindenberg A, Drabant EM, et al. 5-HTTLPR polymorphism impacts human cingulate-amygdala interactions: a genetic susceptibility mechanism for depression. *Nat Neurosci* 2005;8(06):828–834
- 40 Caspi A, Sugden K, Moffitt TE, et al. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science* 2003;301(5631):386–389
- 41 Lonsdorf TB, Weike AI, Nikamo P, Schalling M, Hamm AO, Ohman A. Genetic gating of human fear learning and extinction: possible implications for gene-environment interaction in anxiety disorder. *Psychol Sci* 2009;20(02):198–206
- 42 Lee HJ, Macbeth AH, Pagani JH, Young WS III. Oxytocin: the great facilitator of life. *Prog Neurobiol* 2009;88(02):127–151
- 43 Kirsch P. Oxytocin in the socioemotional brain: implications for psychiatric disorders. *Dialogues Clin Neurosci* 2015;17(04):463–476
- 44 Windle RJ, Shanks N, Lightman SL, Ingram CD. Central oxytocin administration reduces stress-induced corticosterone release and anxiety behavior in rats. *Endocrinology* 1997;138(07):2829–2834
- 45 Kirsch P, Esslinger C, Chen Q, et al. Oxytocin modulates neural circuitry for social cognition and fear in humans. *J Neurosci* 2005;25(49):11489–11493
- 46 Koch SB, van Zuiden M, Nawijn L, Frijling JL, Veltman DJ, Olf M. Intranasal oxytocin normalizes amygdala functional connectivity in posttraumatic stress disorder. *Neuropsychopharmacology* 2016;41(08):2041–2051
- 47 Auyeung B, Lombardo MV, Heinrichs M, et al. Oxytocin increases eye contact during a real-time, naturalistic social interaction in males with and without autism. *Transl Psychiatry* 2015;5:e507
- 48 Lucht MJ, Barnow S, Sonnenfeld C, et al. Associations between the oxytocin receptor gene (OXTR) and affect, loneliness and intelligence in normal subjects. *Prog Neuropsychopharmacol Biol Psychiatry* 2009;33(05):860–866
- 49 Yamasue H, Domes G. Oxytocin and autism spectrum disorders. *Curr Top Behav Neurosci* 2018;35:449–465
- 50 LoParo D, Waldman ID. The oxytocin receptor gene (OXTR) is associated with autism spectrum disorder: a meta-analysis. *Mol Psychiatry* 2015;20(05):640–646
- 51 Yamasue H. Function and structure in social brain regions can link oxytocin-receptor genes with autistic social behavior. *Brain Dev* 2013;35(02):111–118
- 52 Ahima RS, Harlan RE. Charting of type II glucocorticoid receptor-like immunoreactivity in the rat central nervous system. *Neuroscience* 1990;39(03):579–604
- 53 Kovács KJ, Földes A, Sawchenko PE. Glucocorticoid negative feedback selectively targets vasopressin transcription in parvocellular neurosecretory neurons. *J Neurosci* 2000;20(10):3843–3852

- 54 Criado-Marrero M, Rein T, Binder EB, Porter JT, Koren J III, Blair LJ. Hsp90 and FKBP51: complex regulators of psychiatric diseases. *Philos Trans R Soc Lond B Biol Sci* 2018;373(1738):20160532
- 55 Binder EB, Salyakina D, Lichtner P, et al. Polymorphisms in FKBP5 are associated with increased recurrence of depressive episodes and rapid response to antidepressant treatment. *Nat Genet* 2004;36(12):1319–1325
- 56 Willour VL, Chen H, Toolan J, et al; Bipolar Disorder Phenome Group NIMH Genetics Initiative Bipolar Disorder Consortium. Family-based association of FKBP5 in bipolar disorder. *Mol Psychiatry* 2009;14(03):261–268
- 57 Ising M, Depping AM, Siebertz A, et al. Polymorphisms in the FKBP5 gene region modulate recovery from psychosocial stress in healthy controls. *Eur J Neurosci* 2008;28(02):389–398
- 58 Ressler KJ, Mercer KB, Bradley B, et al. Post-traumatic stress disorder is associated with PACAP and the PAC1 receptor. *Nature* 2011;470(7335):492–497
- 59 Falluel-Morel A, Tascau LI, Sokolowski K, Brabet P, DiCicco-Bloom E. Granule cell survival is deficient in PAC1-/- mutant cerebellum. *J Mol Neurosci* 2008;36(1-3):38–44
- 60 Ghzili H, Grumolato L, Thouënnon E, et al. Role of PACAP in the physiology and pathology of the sympathoadrenal system. *Front Neuroendocrinol* 2008;29(01):128–141
- 61 Harmar T, Lutz E. Multiple receptors for PACAP and VIP. *Trends Pharmacol Sci* 1994;15(04):97–99
- 62 Hashimoto H, Shintani N, Baba A. New insights into the central PACAPergic system from the phenotypes in PACAP- and PACAP receptor-knockout mice. *Ann N Y Acad Sci* 2006;1070:75–89
- 63 Mounien L, Do Rego JC, Bizet P, et al. Pituitary adenylate cyclase-activating polypeptide inhibits food intake in mice through activation of the hypothalamic melanocortin system. *Neuropsychopharmacology* 2009;34(02):424–435
- 64 Stroth N, Holighaus Y, Ait-Ali D, Eiden LE. PACAP: a master regulator of neuroendocrine stress circuits and the cellular stress response. *Ann N Y Acad Sci* 2011;1220:49–59
- 65 Dias BG, Ressler KJ. PACAP and the PAC1 receptor in post-traumatic stress disorder. *Neuropsychopharmacology* 2013;38(01):245–246
- 66 Mercer KB, Dias B, Shafer D, et al. Functional evaluation of a PTSD-associated genetic variant: estradiol regulation and ADCYAP1R1. *Transl Psychiatry* 2016;6(12):e978
- 67 Davis M. The role of the amygdala in fear and anxiety. *Annu Rev Neurosci* 1992;15:353–375
- 68 Diener SJ, Nees F, Wessa M, et al. Reduced amygdala responsivity during conditioning to trauma-related stimuli in posttraumatic stress disorder. *Psychophysiology* 2016;53(10):1460–1471
- 69 Giustino TF, Maren S. The role of the medial prefrontal cortex in the conditioning and extinction of fear. *Front Behav Neurosci* 2015;9:298
- 70 Shin LM, Rauch SL, Pitman RK. Amygdala, medial prefrontal cortex, and hippocampal function in PTSD. *Ann N Y Acad Sci* 2006;1071:67–79
- 71 Goodrich M, Armour AC, Panchapakesan K, et al. PAC1R genotype to phenotype correlations in autism spectrum disorder. *Autism Res* 2019;12(02):200–211
- 72 Baron-Cohen S. Do people with autism understand what causes emotion? *Child Dev* 1991;62(02):385–395
- 73 Losh M, Capps L. Understanding of emotional experience in autism: insights from the personal accounts of high-functioning children with autism. *Dev Psychol* 2006;42(05):809–818
- 74 Gaigg SB. The interplay between emotion and cognition in autism spectrum disorder: implications for developmental theory. *Front Integr Neurosci* 2012;6:113
- 75 Fitzpatrick P, Frazier JA, Cochran D, Mitchell T, Coleman C, Schmidt RC. Relationship between theory of mind, emotion recognition, and social synchrony in adolescents with and without autism. *Front Psychol* 2018;9:1337
- 76 James W. What is an emotion? *Mind* 1884;9:188–205
- 77 Lange CG. *The Mechanism of the Emotions*. Boston: Houghton Mifflin; 1912:672–684
- 78 Clarke C. Autism spectrum disorder and amplified pain. *Case Reports in Psychol* 2015;2015:930874
- 79 Gu X, Zhou TJ, Anagnostou E, et al. Heightened brain response to pain anticipation in high-functioning adults with autism spectrum disorder. *Eur J Neurosci* 2018;47(06):592–601
- 80 Vaughan S, McGlone F, Poole H, Moore DJ. A quantitative sensory testing approach to pain in autism spectrum disorders. *J Autism Dev Disord* 2020;50(05):1607–1620
- 81 Friedman BH. Feelings and the body: the Jamesian perspective on autonomic specificity of emotion. *Biol Psychol* 2010;84(03):383–393
- 82 Newman EB, Perkins FT, Wheeler RH. Cannon's theory of emotion: a critique. *Psychol Rev* 1930;37:305–326
- 83 Poquérusse J, Pastore L, Dellantonio S, Esposito G. Alexithymia and autism spectrum disorder: a complex relationship. *Front Psychol* 2018;9:1196
- 84 Sifneos PE. The prevalence of 'alexithymic' characteristics in psychosomatic patients. *Psychother Psychosom* 1973;22(02):255–262
- 85 Hadjikhani N, Zürcher NR, Rogier O, et al. Emotional contagion for pain is intact in autism spectrum disorders. *Transl Psychiatry* 2014;4:e343
- 86 Meng J, Li Z, Shen L. Responses to others' pain in adults with autistic traits: The influence of gender and stimuli modality. *PLoS One* 2017;12(03):e0174109
- 87 Schachter S, Singer JE. Cognitive, social, and physiological determinants of emotional state. *Psychol Rev* 1962;69:379–399
- 88 Tager-Flusberg H. A psychological approach to understanding the social and language impairments in autism. *Int Rev Psychiatry* 1999;11(04):325–334
- 89 Macari S, DiNicola L, Kane-Grade F, et al. Emotional expressivity in toddlers with autism spectrum disorder. *J Am Acad Child Adolesc Psychiatry* 2018;57(11):828–836.e2
- 90 Lazarus RS. *Emotion and Adaptation*. New York: Oxford University Press; 1991
- 91 Green L, Fein D, Joy S, et al. Cognitive functioning in autism. In: Schopler E, Mesibov GB, eds. *Learning and Cognition in Autism*. Current Issues in Autism Boston: Springer; 1995:13–31
- 92 Barrett LF, Mesquita B, Ochsner KN, Gross JJ. The experience of emotion. *Annu Rev Psychol* 2007;58:373–403
- 93 Darwin CR. *The Expression of the Emotions in Man and Animals*. London: John Murray; 1872
- 94 Perkins T, Stokes M, McGillivray J, Bittar R. Mirror neuron dysfunction in autism spectrum disorders. *J Clin Neurosci* 2010;17(10):1239–1243
- 95 Premack D, Woodruff G. Does the chimpanzee have a theory of mind? *Behav Brain Sci* 1978;1:515–526
- 96 Baron-Cohen S. The theory of mind deficit in autism: how specific is it? *British J Dev Psy* 1991;9:301–314
- 97 Baron-Cohen S, Leslie AM, Frith U. Does the autistic child have a "theory of mind"? *Cognition* 1985;21(01):37–46
- 98 Tine M, Lucariello J. Unique theory of mind differentiation in children with autism and Asperger syndrome. *Autism Res Treat* 2012;2012:505393
- 99 Hoogenhout M, Malcolm-Smith S. Theory of mind predicts severity level in autism. *Autism* 2017;21(02):242–252
- 100 Chauhan A, Sahu JK, Jaiswal N, et al. Prevalence of autism spectrum disorder in Indian children: a systematic review and meta-analysis. *Neurol India* 2019;67(01):100–104
- 101 Malhotra S, Vikas A. Pervasive developmental disorders: Indian scene. *J Indian Association of Child Adolescent Mental Health* 2005;1:5
- 102 Rudra A, Banerjee S, Singhal N, Barua M, Mukerji S, Chakrabarti B. Translation and usability of autism screening and diagnostic tools for autism spectrum conditions in India. *Autism Res* 2014;7(05):598–607

- 103 Lord C, Rutter M, Pamela C, et al. ADOS: Autism Diagnostic Observation Schedule. Boston, MA: Hogrefe; 2008
- 104 Rutter M, Le Couteur A, Lord C. ADI-R: Autism Diagnostic Interview-Revised (ADI-R). Los Angeles, CA: Western Psychological Services; 2003
- 105 Lord C, Rutter M, DiLavore P, et al. Autism Diagnostic Observation Schedule. 2nd edition (ADOS-2) Los Angeles, CA: Western Psychological Corporation; 2012
- 106 Le Couteur A, Rutter M, Lord C, et al. Autism diagnostic interview: a standardized investigator-based instrument. *J Autism Dev Disord* 1989;19(03):363–387
- 107 Schopler E, Reichler RJ, DeVellis RF, Daly K. Toward objective classification of childhood autism: Childhood Autism Rating Scale (CARS). *J Autism Dev Disord* 1980;10(01):91–103
- 108 Schopler E, Van Bourgondien ME, Wellman GJ, et al. CARS-2: Childhood Autism Rating Scale. Second Edition Los Angeles, CA: West Psy Ser; 2010
- 109 Gilliam JE. GARS-3: Gilliam Autism Rating Scale. Third edition Austin, TX: PRO-ED; 2014
- 110 Rutter M, Bailly A, Lord C. The Social Communication Questionnaire. Los Angeles: West Psy Ser; 2003
- 111 Juneja M, Mishra D, Russell PS, et al; INCLIN Study Group. INCLIN Diagnostic Tool for Autism Spectrum Disorder (INDT-ASD): development and validation. *Indian Pediatr* 2014;51(05):359–365
- 112 National Institute for Mentally Handicapped, Ministry of Social Justice and Empowerment, Department of Empowerment of Persons with Disabilities. (Divyangjan) Government of India. Indian Scale for Assessment of Autism (ISAA) Test Manual New Delhi 2009
- 113 de Bildt A, Sytema S, Ketelaars C, et al. Interrelationship between Autism Diagnostic Observation Schedule-Generic (ADOS-G), Autism Diagnostic Interview-Revised (ADI-R), and the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) classification in children and adolescents with mental retardation. *J Autism Dev Disord* 2004;34(02):129–137
- 114 Wong CM, Singhal S. INDT-ASD: an autism diagnostic tool for Indian children. Developmental pediatrician's perspective. *Indian Pediatr* 2014;51(05):355–356
- 115 Raina SK, Kashyap V, Bhardwaj AK, Kumar D, Chander V. Prevalence of autism spectrum disorders among children (1-10 years of age) - findings of a mid-term report from Northwest India. *J Postgrad Med* 2015;61(04):243–246